IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	**MDL No. 2:14-mn-02502-RMG** **This Document Relates to All Actions**

PFIZER INC.'S SUPPLEMENTAL BRIEF PURSUANT TO CMO 53 IN FURTHER SUPPORT OF ITS MOTION TO EXCLUDE AS PREEMPTED PLAINTIFFS' CLAIMS THAT LIPITOR IS NOT EFFECTIVE FOR PRIMARY PREVENTION IN WOMEN

Pursuant to Case Management Order No. 53, this memorandum addresses whether, "to the extent that the Court finds any claims regarding efficacy and based on Lipitor's label are preempted by federal law, are Plaintiffs' claims regarding efficacy and based on Lipitor's advertising also preempted?" [1255] As explained below, yes, the federal statutes and regulations governing prescription drug labeling and advertising, together with relevant preemption decisions, including *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011), *Mutual Pharmaceutical Co. v. Bartlett*, 133 S. Ct. 2466 (2013), and *Drager v. PLIVA USA, Inc.*, 741 F.3d 470 (4th Cir. 2014), confirm that Plaintiffs' efficacy claims based on Pfizer's advertising are preempted for the same reasons that their efficacy claims based on the Lipitor label are preempted.

Plaintiffs' efficacy claims related to the FDA-approved labeling for Lipitor, which under federal law includes its advertising, seek to impose liability under state law for selling and marketing Lipitor for primary prevention in both men and women, an FDA-approved use. Plaintiffs' claims are based on their disagreement with FDA's interpretation of the clinical trial data that FDA determined supported gender-neutral approval of Lipitor for primary prevention. Both before and after the Supreme Court's decision in *Mensing*, courts have held that claims related to prescription drug advertising consistent with a medicine's FDA-approved

label are preempted. Pfizer could not independently change its FDA-approved indication for Lipitor for primary prevention in the way Plaintiffs claim it should have been changed to avoid liability under state law. It would therefore be impossible for Pfizer to satisfy both its obligation under federal law to sell and advertise Lipitor consistent with its FDA-approved indication and an alleged state-law obligation to not advertise Lipitor for primary prevention in women. All of Plaintiffs' efficacy claims are thus preempted.

I. Advertising Claims Are Preempted to the Same Extent as Labeling Claims

Plaintiffs' claims based on Pfizer's marketing and advertising of Lipitor for primary prevention are preempted because their claims based on the labeling of Lipitor for primary prevention are preempted. Under federal law, prescription drug labeling encompasses advertising for the drug. *See* 21 U.S.C. § 321(m); 21 C.F.R. § 202.1(l)(2). Just as the labeling issued with an FDA-approved medicine must conform to the label approved by FDA, so must all advertising for the medicine. *See Strayhorn v. Wyeth Pharms., Inc.*, 737 F.3d 378, 394 (6th Cir. 2013).

> Under the [Food, Drug, and Cosmetics Act (FDCA)], "labeling" embraces "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). The Supreme Court has held that the first clause "clearly embraces advertising or descriptive matter that goes with the package in which the articles are transported." *Kordel v. United States,* 335 U.S. 345, 349–50, 69 S.Ct. 106, 93 L.Ed. 52 (1948). With respect to the second clause, "[o]ne article or thing is accompanied by another when it supplements or explains it.... No physical attachment one to the other is necessary." *Id.* Furthermore, the Code of Federal Regulations includes brochures, booklets, mailings, catalogues, films, sound recordings, and literature, among other things, in the definition of "labeling." 21 C.F.R. § 202.1(l)(2).[1] Such labeling must be consistent with the drug's approved

[1] The regulation provides, in full: "(l)(2) Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the 'Physicians Desk Reference') for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act." 21 C.F.R. § 202.1(l)(2).

> labeling. 21 C.F.R. § 201.100(d)(1); *see also* 21 C.F.R. § 202.1(e)(4) (prohibiting advertisements that "recommend or suggest" any use that is not in the labeling approved by the FDA).

Id. at 394. "In essence, virtually all communication with medical professionals concerning a drug constitutes labeling." *Del Valle v. PLIVA, Inc.*, 2011 WL 7168620, at *4 (S.D. Tex. Dec. 21, 2011), *report and recommendation adopted by Del Valle v. Qualitest Pharms., Inc.*, 2012 WL 2899406 (S.D. Tex. June 22, 2012), *aff'd sub nom. Lashley v. Pfizer, Inc.*, 750 F.3d 470 (5th Cir. 2014).

Thus, "[b]ecause … advertising and promotional materials are considered labeling, and because labeling is limited by federal law to the information contained in the [FDA-approved] labeling," claims based on advertising are preempted to the same extent as labeling claims. *Strayhorn*, 737 F.3d at 394; *accord Drager*, 741 F.3d at 479; *Schrock v. Wyeth, Inc.*, 727 F.3d 1273, 1287-88 (10th Cir. 2013). In particular, a drug manufacturer cannot be held liable under state law for advertising consistent with its FDA-approved label where, as here, it could not have independently changed the label. *Drager*, 741 F.3d at 479. Under the Supreme Court's decision in *Mensing*, even if a manufacturer's "promotional … materials …. are false or misleading," state-law causes of action are preempted where the manufacturer "has no authority to add or remove information from its materials … to make its representations complete or truthful." *Id.*

As set forth in Pfizer's prior briefing and below, Plaintiffs' efficacy claims based on the Lipitor label are preempted. [970 at 31-35; 1090 at 13-16] Under *Mensing*, *Bartlett*, and *Drager*, their efficacy claims based on marketing and advertising communications are preempted for the same reasons.

II. Plaintiffs' Claims Regarding Pfizer's Advertising of Lipitor Are Preempted

A. Pfizer's Inability to Unilaterally Change the FDA-Approved Indication for Primary Prevention Bars Plaintiffs' Advertising Claims

Plaintiffs' claims regarding the efficacy of Lipitor for primary prevention in women that are based on Pfizer's advertising of Lipitor are preempted. It is impossible for Pfizer to comply with both (i) its federal obligation to use the FDA-approved label and (ii) an alleged state-law

duty to not advertise Lipitor for primary prevention in women or to make statements about efficacy in women that are inconsistent with the approved label.

Plaintiffs' advertising-related claims, like their labeling claims, are based on Plaintiffs' and their experts' disagreement with FDA's decision to grant gender-neutral approval for primary prevention in 2004 based on data from the ASCOT trial. Plaintiffs have not alleged and none of their experts opines that Pfizer engaged in any marketing or advertising of Lipitor that was "off-label" or inconsistent with the FDA-approved Lipitor label. Although Dr. Abramson has offered opinions in support of off-labeling marketing claims in other pharmaceutical litigations, he admits that he does not do so here. Abramson Tr. (Ex. 5) at 112:7-15. Instead, to the extent Dr. Abramson opines that Pfizer's marketing of Lipitor for women for primary prevention was "inaccurate, false and misleading," Abramson Rpt. (Ex. 1) at 111, he relies on his disagreement with FDA's approval of Lipitor for primary prevention in both men and women based on ASCOT and the FDA-approved language in the label relating to that indication. *See, e.g.*, *id.* ¶¶ 18, 20, 22, 478; Abramson Tr. (Ex. 5) at 18:4-19:14, 32:2-33:5.[2] Nor have Plaintiffs alleged that Pfizer's advertising for Lipitor violated the regulations governing the content of prescription drug advertising. *See, e.g.*, 21 C.F.R. § 202.1(e)(1)-(7). Dr. Fleming, Plaintiffs' only regulatory expert, does not offer any opinion about the marketing or advertising of Lipitor. *See* Fleming Tr. (Ex. 6) at 315:23-316:1.

The application of impossibility preemption in this context "hing[es] … on the availability of [the Changes Being Effected (CBE)] procedure," which allows a manufacturer in certain limited circumstances to change a medicine's FDA-approved label without first seeking FDA approval. *In re Celexa and Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41 (1st

[2] Dr. Abramson also conceded that although he devoted approximately 75 pages of his expert report to an opinion that Pfizer engaged in false and inaccurate marketing of Lipitor to women, he did not know "whether any of the documents [he] cited and relied upon for [his] opinions are documents that were used externally by any person in marketing or promoting Lipitor." Abramson Tr. (Ex. 5) at 614:16-615:2. He admitted that he never reviewed the files that Pfizer produced in this litigation that contained Lipitor advertising materials that Pfizer actually used and were submitted to FDA. *Id.* at 616:4-11; *see also* 21 C.F.R. § 314.81(b)(3).

Cir. 2015). Where "the CBE process was not open to [defendant] for the sort of change required by" a plaintiff's state-law claims, those state-law claims are preempted. *Mensing*, 131 S. Ct. at 2575-76. In addition, the Supreme Court has rejected the argument that a conflict preemption analysis in a case in which the CBE procedure was not available "should take into account … *possible* actions by the FDA and the … manufacturer" that could have allowed the manufacturer to comply with state-law obligations even where it could not have unilaterally changed the label. *Id.* at 2578 (emphasis added). The Court in *Mensing* confirmed that a showing that a manufacturer could have *requested* a label change from FDA does not override preemption where the manufacturer could not independently change the label through a CBE. *Id.* at 2578-80. The Court also specifically addressed the possibility that a manufacturer of a generic medicine, although unable to use the CBE procedure to unilaterally change safety information in the drug's label, could have complied with both its federal obligation to use that label and its state-law obligation to provide an adequate warning by issuing other communications, such as a "Dear Doctor" letter, to warn doctors about an alleged safety issue. *Mensing*, 131 S. Ct. at 2576. The Court rejected that argument, holding that "Dear Doctor letters qualify as 'labeling'" and thus "must be consistent with and not contrary to the drug's approved labeling." *Id.* (quotation omitted).

"Key to the *Mensing* decision was the Court's deference to the FDA's broad-definition of 'labeling.'" *Schrock*, 727 F.3d at 1287. Thus, because "the same federal regulatory scheme" that precludes independent label changes where the CBE procedure is not available "applies to a broad array of communications" that are included within the definition of "labeling," claims alleging that a manufacturer should have changed its advertising for a medicine are preempted to the same degree as claims based on the FDA-approved label. *Id.* at 1288; *accord Drager*, 741 F.3d at 479; *Johnson v. Teva Pharm. USA, Inc.*, 2012 WL 1866839, at *3 (W.D. La. May 21, 2012), *aff'd*, 758 F.3d 605 (5th Cir. 2014).[3] *Drager*, like *Mensing*, was a failure-to-warn case

[3] *See also, e.g.*, *In re Yasmin and Yaz (Drospirenone) Mktg., Sales Practices & Prods. Liab. Litig.*, 2015 WL 7272766, at *5 (S.D. Ill. Nov. 18, 2015); *Gardley-Starks v. Pfizer, Inc.*,

involving a generic medicine as to which the CBE procedure was not available to the manufacturer to unilaterally change the label. Plaintiff argued that her state-law claims based on advertising activities were nevertheless not preempted because "manufacturers voluntarily elect to make certain assertions about their products in … promotional materials and … as a result the manufacturers themselves, not the law, impose the obligation to conform to those assertions." *Drager*, 741 F.3d at 479. The Fourth Circuit rejected this argument because "the content of [the] product descriptions and other assertions is mandated by federal law," and the manufacturer "[could not] change its written materials" without FDA approval. *Id.*

Likewise, in *Strayhorn*, the Sixth Circuit held that plaintiffs' claims involving advertising for the generic medicines at issue were preempted because the generic manufacturer defendants could not use the CBE procedure to unilaterally change the labeling of their products to add the safety information plaintiffs claimed was missing. *Strayhorn*, 737 F.3d at 394. Similarly, in *Celexa*, the First Circuit held that plaintiffs' marketing and consumer fraud claims involving an approved indication were preempted because the brand manufacturer could not "use the CBE procedure to alter the FDA label in the manner that plaintiffs allege is necessary so as to render it not 'misleading.'" *Celexa*, 779 F.3d at 43. Here too, because it would be impossible for Pfizer to independently change the FDA-approved primary prevention labeling for Lipitor under the CBE process, claims alleging that Pfizer should have taken some different action with respect to its advertising regarding the efficacy of Lipitor for primary prevention are likewise preempted.[4]

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917 F. Supp. 2d 597, 605-06, 608-09 (N.D. Miss. 2013); *Truddle v. Wyeth, LLC*, 2012 WL 3338715, at *2-3 (N.D. Miss. Aug. 14, 2012); *Rojas v. Teva Pharms. USA, Inc.*, 920 F. Supp. 2d 772, 777-78 (S.D. Tex. 2013); *Eckhardt v. Qualitest Pharms. Inc.*, 858 F. Supp. 2d 792, 797, 799 (S.D. Tex. 2012), *aff'd,* 751 F.3d 674 (5th Cir. 2014).

[4] Even if Plaintiffs were alleging off-label marketing or some other violation of the FDA regulations governing prescription drug advertising, there is no private right of action to bring such claims unless they are based on "specific representations … that are literally false, misleading, or contained a material omission." *In re Epogen and Aranesp Off-Label Mktg. & Sales Practices Litig.*, 2009 WL 1703285, at *4 (C.D. Cal. June 17, 2009), *aff'd sub nom. United Food & Commercial Workers Cent. Penn. & Reg'l Health & Welfare Fund v. Amgen*, 400 Fed. Appx. 255 (9th Cir. Oct. 21, 2010); *see* 21 U.S.C. § 337(a). Plaintiffs have not identified such representations just as they have not identified information that renders the Lipitor labeling and

A pre-*Mensing* preemption case involving Lipitor is also directly relevant. In *Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228 (S.D. Fla. 2007), plaintiffs alleged "that there is no scientific support for the claim that Lipitor reduces the risk of heart disease in women or elderly patients who do not already have heart disease or diabetes," and they brought consumer fraud claims based on Pfizer's advertising for Lipitor for reduction of the risk of heart disease. *Id.* at 1230. The action was dismissed on the merits through a series of decisions, including this decision holding that "plaintiffs' post-July 2004 claims" – claims post-dating FDA's approval of Lipitor for primary prevention – "do not survive Pfizer's motion to dismiss because they are preempted by federal law." *Id.* at 1234.

> In July of 2004, the FDA approved Lipitor to reduce the risk of heart attacks in patients, including women and the elderly, with multiple risk factors for coronary heart disease. Its FDA approved label specifically includes this indication. Accordingly, **any advertisements that stated or implied that Lipitor reduced the risk of heart disease or heart attacks simply marketed an approved use for the drug.** Although I recognize that Lipitor was not approved to reduce the risk of heart attacks in all patients, **the alleged advertisements derive from, and largely comport with, the approved label**. For this reason, **the plaintiffs' efforts to hold Pfizer liable for the advertisements conflicts with the FDA's jurisdiction over drug labeling**, and specifically its approval of Lipitor to reduce the risk of heart disease in some patients. Those claims are therefore preempted by federal law.

Id. at 1234 (emphasis added).[5]

Plaintiffs' claims based on Pfizer's advertising, just like those in *Prohias*, relate to advertisements for primary prevention that "derive from … the approved label." *Id.* Here, as there, Plaintiffs' state-law claims based on Pfizer's advertising conflict with FDA's jurisdiction over drug labeling and with Pfizer's obligation to comply with the labeling approved by FDA.

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advertising related to primary prevention "false, misleading, or unsupported" and would thus require a unilateral CBE label change. 21 C.F.R. § 314.70(c)(6)(iii)(D).

[5] *See also Prohias v. Pfizer, Inc.*, 485 F. Supp. 2d 1329 (S.D. Fla. 2007); *Prohias v. Pfizer, Inc.*, No. 1:05-cv-22658, Order on Motion for Summary Judgment [Dkt. 88] (S.D. Fla. Aug. 16, 2007). After the court granted summary judgment dismissing claims regarding pre-2004 written advertising, plaintiffs voluntarily dismissed with prejudice their remaining claims. *See* Final Order of Dismissal With Prejudice and Closing Case [Dkt. 99] (S.D. Fla. Jan. 9, 2008).

The Supreme Court's subsequent decision in *Wyeth v. Levine*, 555 U.S. 555 (2009), does not affect the analysis and applicability of *Prohias*. *Levine* involved the availability of the CBE process to strengthen a safety warning to reflect new information. 555 U.S. at 569-70. It did not address claims challenging an FDA-approved indication based on the same information considered by FDA in approving the indication. *Mensing* confirms that such claims are preempted because Pfizer could not have changed the indication through the CBE process. *See Mensing*, 131 S. Ct. at 2579.[6]

B. A Claim that Pfizer Should Have Stopped Advertising Is Also Preempted

Plaintiffs cannot avoid preemption by arguing that Pfizer should have stopped advertising Lipitor as effective for women for primary prevention. In *Mutual Pharmaceutical Co. v. Bartlett*, the Supreme Court rejected "as incompatible with [its] pre-emption jurisprudence" the argument that a generic pharmaceutical manufacturer could have simultaneously satisfied its state-law and federal-law labeling obligations by no longer making and selling the medicine. 133 S. Ct. 2466, 2477 (2013). Impossibility preemption "presume[s] that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability. Indeed, if the option of ceasing to act defeated a claim of impossibility, impossibility pre-emption would be 'all but meaningless,'" since any conflict between state and

[6] Even assuming that Prof. Wells's ASCOT re-analysis were not subject to exclusion under *Daubert*, it not only could not support a unilateral label change under the CBE process for the reasons Pfizer identified in its earlier briefing, but it also would not support an independent claim for false or misleading advertising. "The information included in the labeling of a … drug reflects a determination by the FDA that the information is not 'false or misleading.' 21 C.F.R. 314.125(b)(6)." *Prohias*, 490 F. Supp. 2d at 1235. The record confirms that the FDA-approved labeling reflects consideration of the then-existing limitations in efficacy data for women, including a finding of heterogeneity by gender under at least one statistical analysis used by FDA when it evaluated the ASCOT data. [970 at 9-11, 18 & n. 30] *See also* Abramson Rpt. (Ex. 1) ¶ 369. The section of the label describing the ASCOT trial data has always included the following statement: "Due to the small number of events, results for women were inconclusive." July 2004 Lipitor Label (Ex. 32). The FDA-approved indication itself, however, is gender neutral and is not misleading as a matter of law. *Prohias*, 490 F. Supp. 2d at 1235. So too is advertising consistent with that indication.

federal law could always "be[] avoided if the regulated actor had simply ceased acting." *Id.* (quoting *Mensing*, 131 S.Ct. at 2579).

Plaintiffs' suggestion that Pfizer should have simply stopped marketing Lipitor as effective for women for primary prevention based on information, such as Prof. Wells's ASCOT re-analysis, that would not support a unilateral label change through the CBE process, would effectively require Pfizer to withdraw from conduct that is regulated and permissible under federal law to avoid a conflict between state and federal law. Under *Bartlett*, "courts may not avoid preempting a state law by imposing liability on a generic manufacturer for choosing to continue selling its product." *Drager*, 741 F.3d at 476. The same reasoning applies here. Under federal law, the selling of a prescription medicine involves the distribution of FDA-approved labeling for the medicine, and that labeling includes advertising communications.

Thus, marketing and advertising that is consistent with the FDA-approved label is protected under *Bartlett* where, as here, the manufacturer could not have independently changed the label. Just as a state cannot impose, through a tort action, its own scientific requirements to prohibit selling a medicine that FDA has determined may be sold pursuant to its approved labeling, a state also cannot impose idiosyncratic standards to prevent marketing a medicine to a particular group of patients for whom FDA has determined the medicine is safe and effective pursuant to its approved labeling.

CONCLUSION

For the foregoing reasons, as well as those set forth in Pfizer's prior briefing and at the hearing on this motion, this Court should grant Pfizer's motion to exclude as preempted Plaintiffs' claims and expert testimony that Lipitor is not effective for or should not be approved for primary prevention in women, including claims related to Pfizer's advertising.

DATED: December 1, 2015

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CERTIFICATE OF SERVICE

I hereby certify that, this 1st day of December 2015, I have electronically filed a copy of the above and foregoing with the Clerk of the Court using the ECF system, which sent notification of such filing to counsel of record.

/s/ Mark S. Cheffo
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